
بسم الله الرحمن الرحيم

Haemodialysis (HD)
Principles and Techniques

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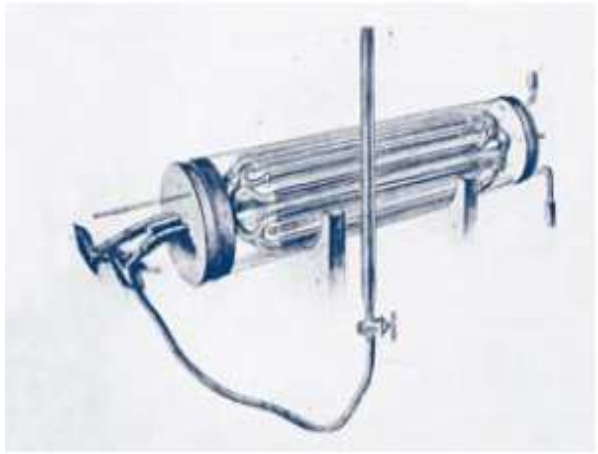
AGENDA

- ✓ HD: History , Present & Future.
- ✓ Introduction.
- ✓ Uremic Toxins.
- ✓ Mechanisms Of Solute Removal.
- ✓ HD:
  - * Principle.
  - * Apparatus.
  - * Membranes.
  - * Concentrate solution.
  - * Water Treatment System.
- ✓ HF and HDF.

HISTORY



John Abel: 1913

- From Johns Hopkins.
- Develops primitive dialysis system.
- Testing on animals with no success.

HISTORY

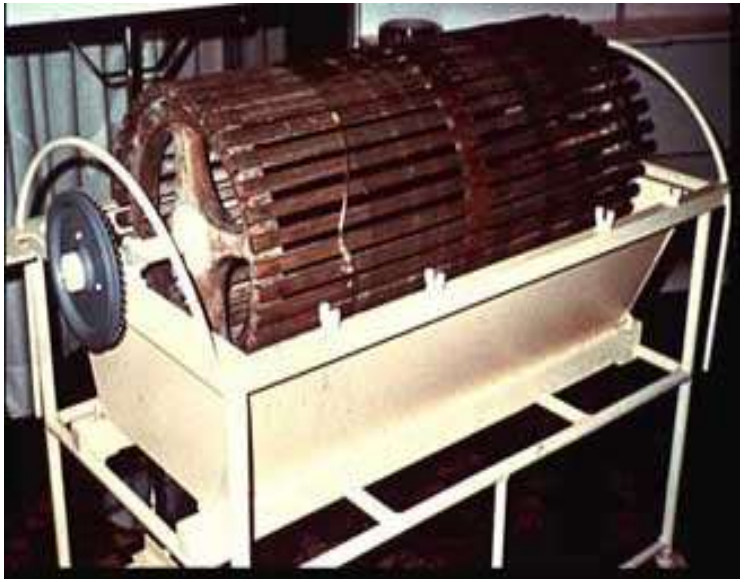
George Haas: 1926

- From Giessen, Germany.
- The first who tried it on human with ARF.
- He used a tubular device made of collodion,

cannulation of the radial and carotid arteries and the portal vein and hirudin for anticoagulation.

- Patient died as no enough clearance.

HISTORY



Willem Kolff: 1933-1945

- From Netherland.
- Started his experimentation 1933.
- Invented the "drum dialyzer".
- Treated 16 patient with ARF who did not survived it in 1943.
- Treated first female patient with ARF in 1945 who survived it.
- Distributed 6 machines to western world.

HISTORY

PRESENT

FUTURE

Sorbents, Nanotechnology, Wearable Artificial Kidney

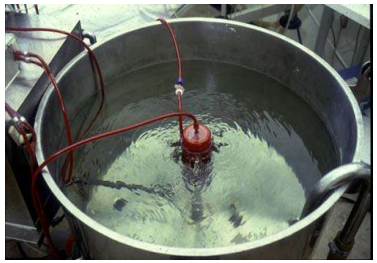
- Use of sorbents to absorb nondialyzable molecules will test the relevance as uremic toxins of the many protein-derived substances that accumulate in the plasma of uremic patients.
- Nanotechnological approaches to dialysis therapy are under intensive Investigation.
- A study has reported the successful short-term use of a wearable artificial kidney.

Portable HDx

Automated, wearable, artificial kidney

INTRODUCTION

- Despite the widespread use of peritoneal dialysis and renal transplantation, hemodialysis (HD) remains the main renal replacement therapy in most countries worldwide.
- More than 1.7 million patients are currently treated with HD in about 28,500 dialysis units worldwide.
- Despite significant advances in our understanding of the biology of CKD and the risk factors for poor outcome on HD and improved dialysis technology, the annual mortality in HD patients varies from 10% to 25% internationally, depending on demographic and genetic factors.

Organic Uremic Solutes

Free Water-Soluble Low-Molecular-Weight Solutes	MW	Protein-Bound Solutes	MW	Middle Molecules	MW
Guanidines		**AGE**		**Cytokines**	
ADMA	202	3-Deoxyglucosone	162	Interleukin-1β	32000
Argininic acid	175	Fructoselysine	308	Interleukin-6	24500
Creatinine	113	Glyoxal	58	Tumor necrosis factor-α	26000
Guanidine	59	Pentosidine	342	**Peptides**	
Methylguanidine	73	**Hippurates**		Adrenomedulin	5729
Peptides		Hippuric acid	179	ANP	3080
β-Lipotropin	461	**Indoles**		β-2-Microglobulin	11818
Polyols		Indoxyl sulfate	251	β-Endorphin	3465
Erythritol	122	Melatonin	126	Cholecystokinin	3866
Myoinositol	180	Quinolinic acid	167	Cystatin C	13300
Sorbitol	182	**Phenols**		Delta sleep-inducing peptide	848
Threitol	122	Hydroquinone	110	Hyaldronic acid	25000
Purines		P-Cresol	108	Leptin	16000
Cytidine	234	Phenol	94	Neuropeptide Y	4272
Hypoxanthine	136	**Polyamines**		PTH	9225
Uracil	112	Putrescine	88	Retinol-binding protein	21200
Uric acid	168	Spermidine	145	**Others**	
Xanthine	152	Spermine	202	Complement factor D	23750
Pyrimidines		**Others**			
Orotic acid	174	Homocysteine	135		
Thymine	126				
Uridine	244				
Ribonucleosides					
1-Methyladenosin	281				
Pseudouridine	244				
Xanthosine	284				
Others					
Malondialdehyde	71				
Oxalate	90				
Urea	60				

Solute Removal by Dialysis and the Natural Kidney

	Natural Solute Kidney	Hemodialysis-Standard Flux	Hemodialysis-High Flux	CAPD
Urea L/wk:	750 →	130 →	130 →	70 →
Vitamin B_{12} L/wk:	1,200	30	60	40
Inulin L/wk:	1,200	10	40	20
β_2-microglobulin:	1,000 →	0 →	300 →	250 →

CAPD, continuous ambulatory peritoneal dialysis.

[From Keshaviah P. Adequacy of CAPD: a quantitative approach. *Kidney Int* 1992;42(Suppl 28):S160-S164.]

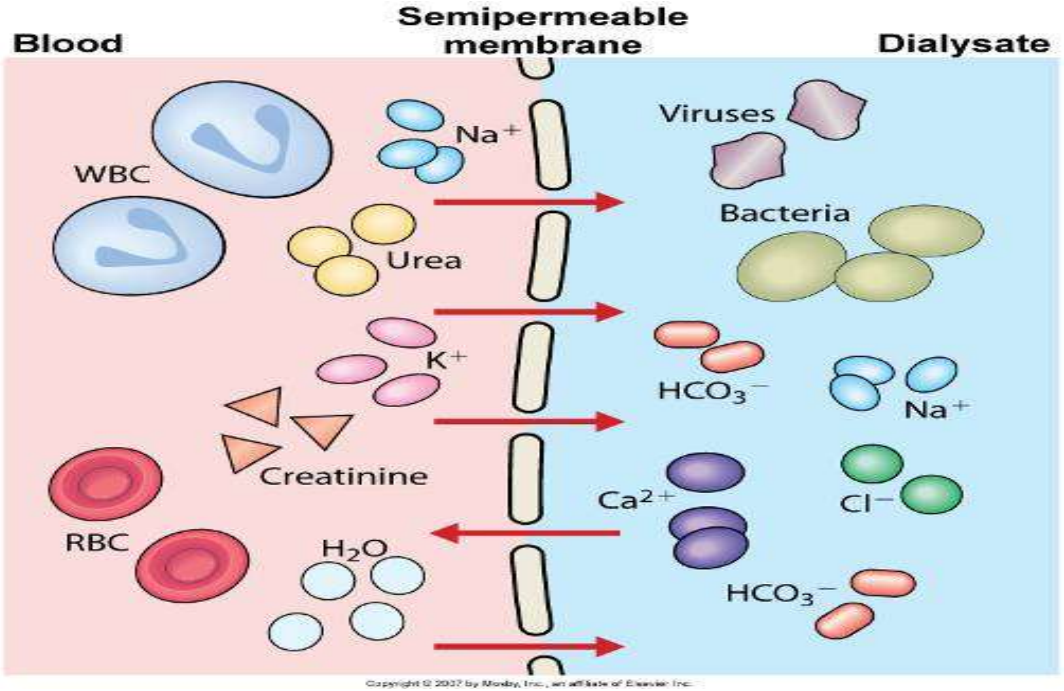
Mechanisms of Solute Transport:

- Solute removal via semipermeable membrane during extracorporeal renal replacement therapy occurs by :

A - Diffusion (HD).

B - Convection (HF).

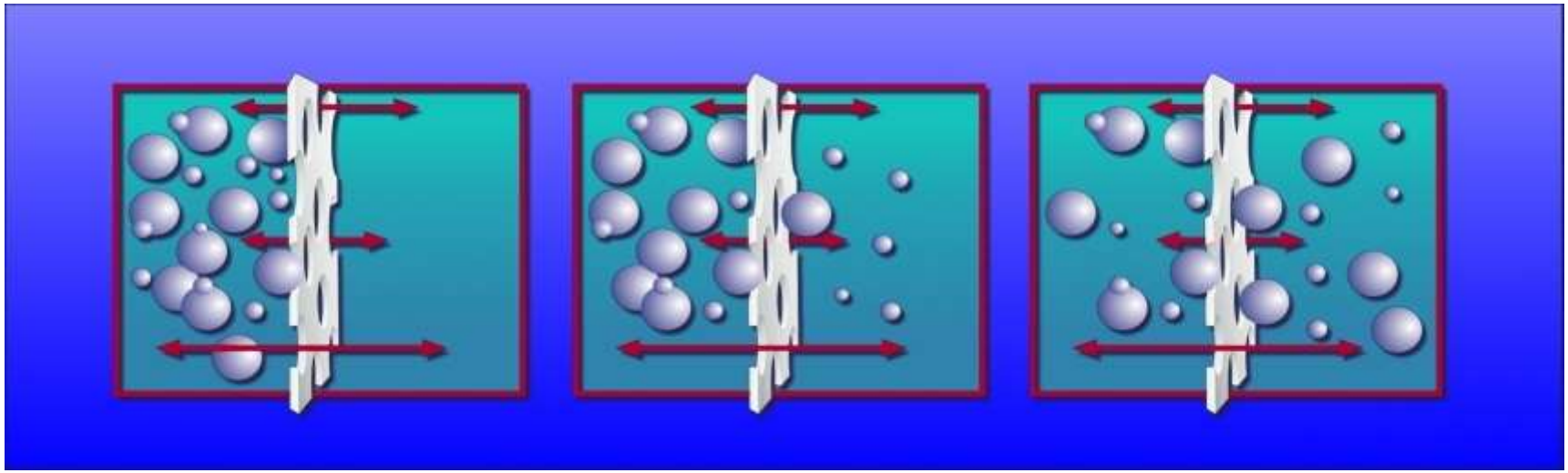
C - Adsorption (HP).



A) DIFFUSION

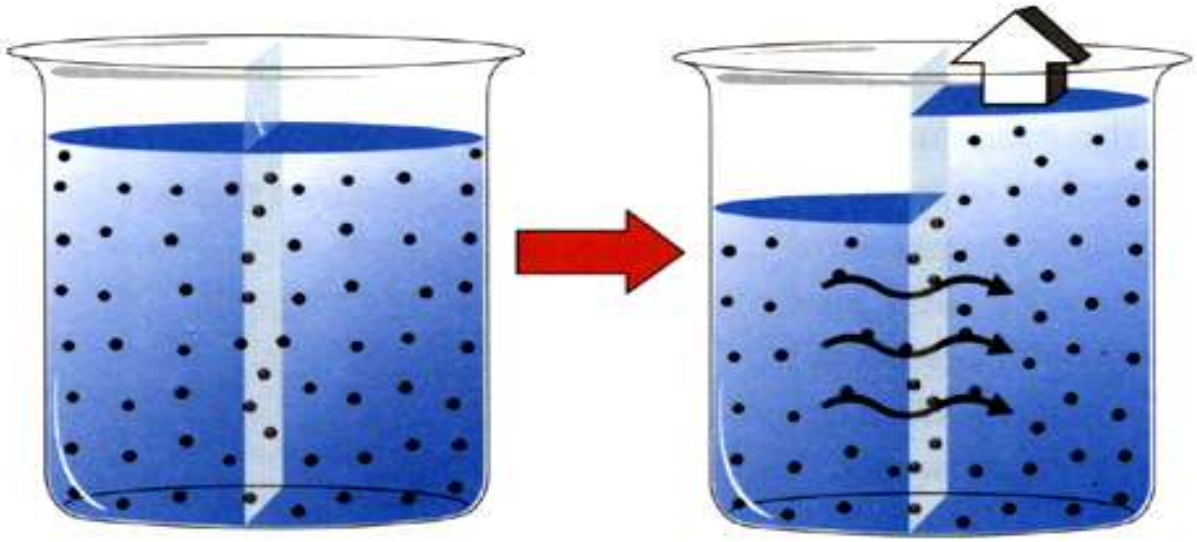
- **Diffusion** is a transport process by which solutes move passively down its concentration gradient from an area of greater concentration to an area of lesser concentration.
- It is particularly effective in the transport of small solutes such as urea, potassium.
- The random movement (Brownian Movement) of solutes is dependant on the;
  1) Concentration gradient 2) Molecular weight 3) Membrane resistance
- **Hemodialysis (HD)** removes solutes primarily by diffusion.

Start End

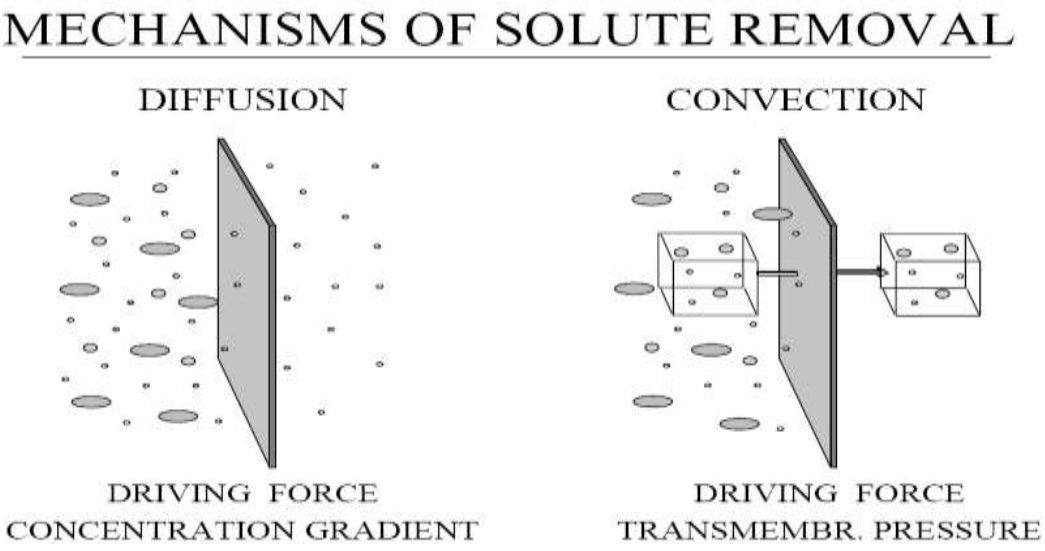


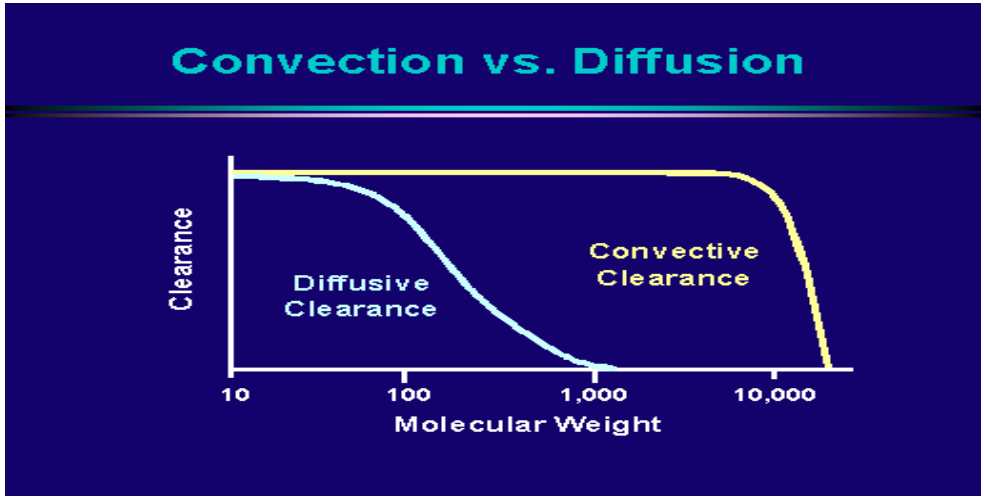
B) CONVECTION

- It occurs as a result of hydrostatic pressure gradient across the membrane. Solutes that are dissolved in the water are transported passively with the water movement (solvent drag).
- The amount of solute removed by convection is dependent on:
  1) the amount of plasma water transported across the membrane.
  2) the size of the solute relative to the pore size of the membrane.
- **Hemofiltration** (HF) removes solutes by convection.



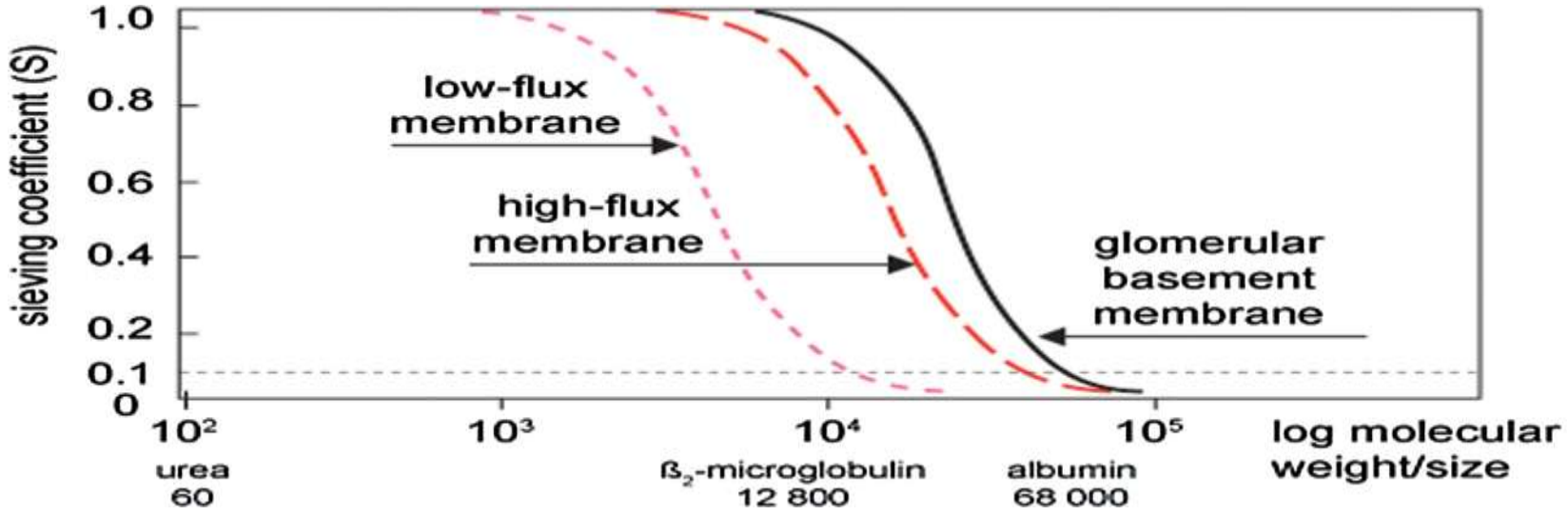
Diffusion vs Convection





SIEVING COEFFICIENT

- The propensity for impedance of any solute is described by the sieving coefficient, this coefficient equals the ratio of the solute concentration in the filtrate to that in the arterial plasma.
- A sieving coefficient of **one** denotes a solute which passes completely unimpeded, whereas a solute which is completely rejected has a coefficient of **zero**.



Ledebo I , Blankestijn P J NDT Plus 2010;3:8-16

C) Adsorption

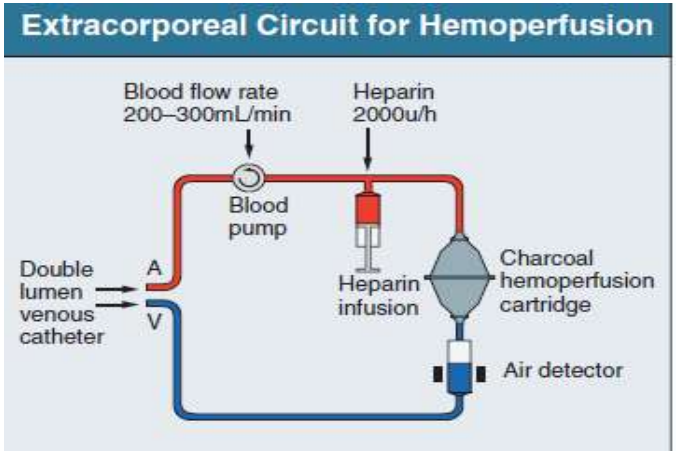
- Hemoperfusion:

  - Is the removal of solutes from blood by adsorption onto materials, such as charcoal or resins, in the extracorporeal circuit.

- Charcoal hemoperfusion:

  - Is effective in clearing protein-bound compounds " P-cresol".

  - It is primarily used for the removal of drugs in acute poisoning, although it has also been used to a limited extent for the treatment of end-stage renal disease.



Fluid Removal

- Ultrafiltration (UF) :

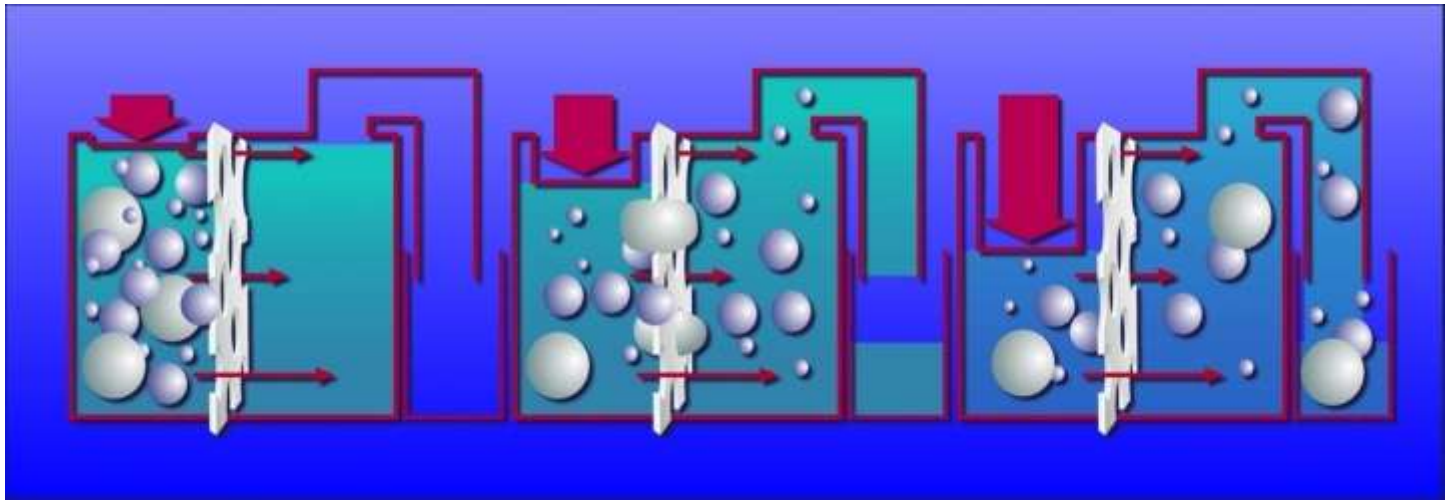
  - Controlled fluid removal by manipulation of hydrostatic pressure gradient across the membrane which is generated by the dialysis machine.

  - UF uses:

  • Positive pressure: Pressure exerted by the blood flowing through the dialyzer.

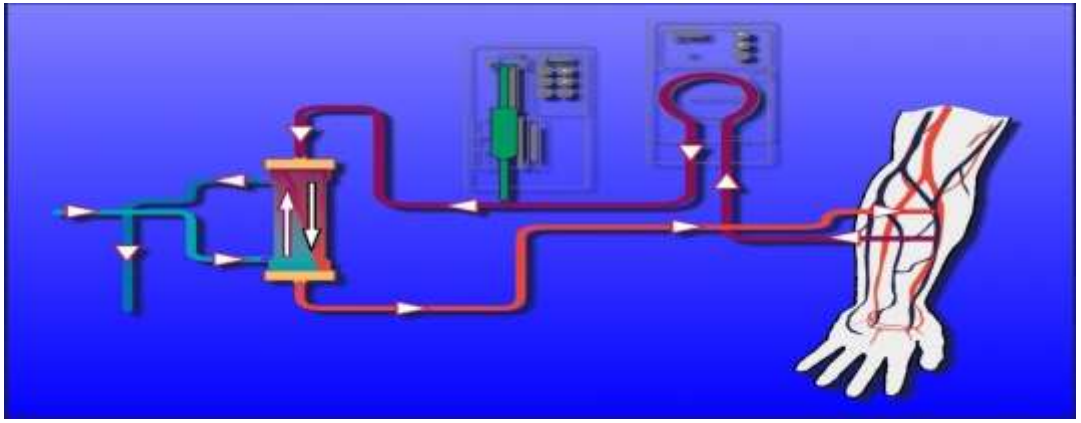
  • Negative pressure: Pressure applied to the dialysate side by the machine.

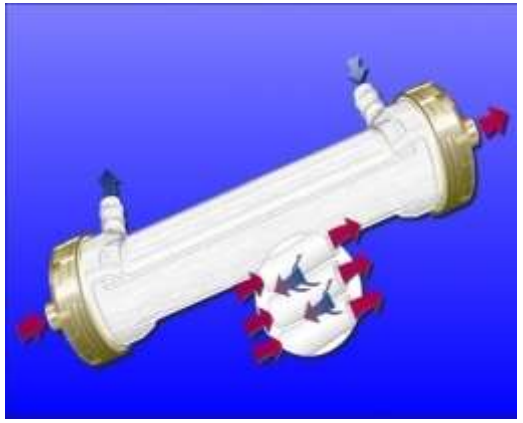
  - It will pull fluid and solutes, as long as they can pass the membrane, from blood compartment to dialysate compartment ⟶ drain.

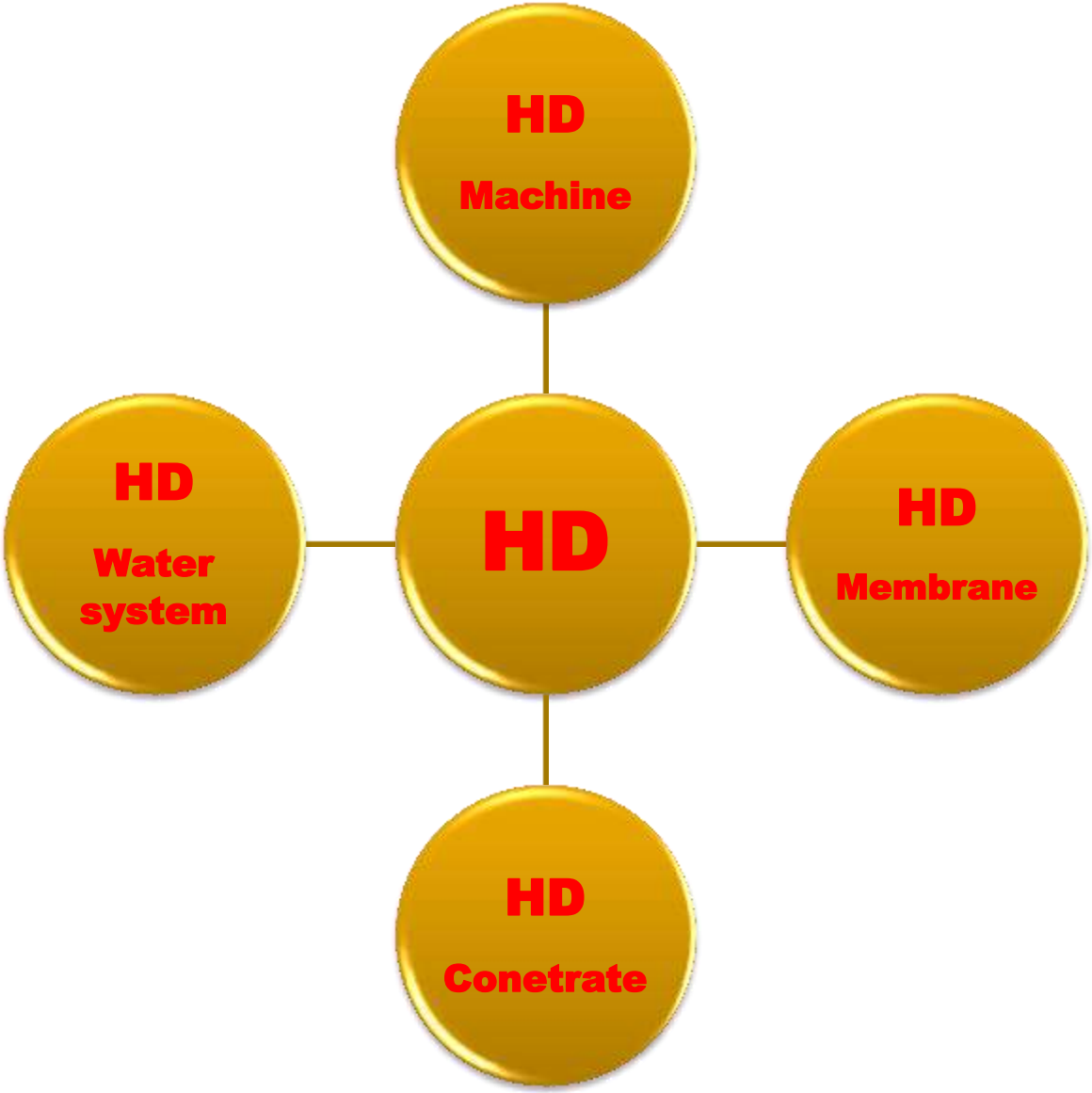


Hemodialysis (HD) Principle

- HD is a method for removing excess water, waste products such as urea, correct fluid/electrolyte/acid base imbalances and to treat drug overdose.
- The HD machine pumps the patient's blood and the dialysate through the dialyzer in countercurrent fashion to maximize clearance of solutes.
- The dialyzer is composed of thousands of tiny synthetic hollow fibers. The fiber wall acts as the semipermeable membrane.
- Blood flows through the fibers, dialysis solution flows around the outside of the fibers, and water and solutes move between these two solutions.
- The cleaned blood is then returned via the circuit back to the body.






HD
Machine
HD
Water system
HD
HD
Membrane
HD
Conetrate

A) Hemodialysis Apparatus

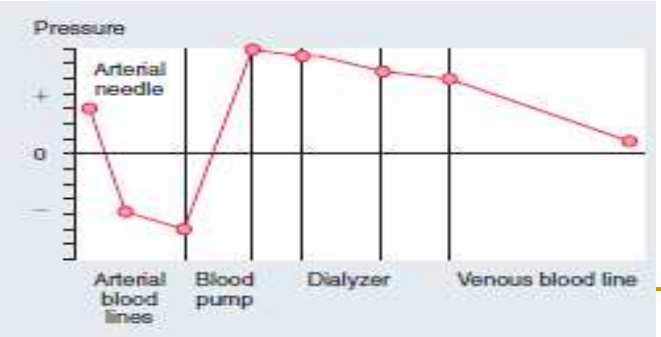
- ✓ The HD equipment has blood and dialysate circuit components.
- ✓ The HD machine has safety and monitoring devices to ensure safe operation.

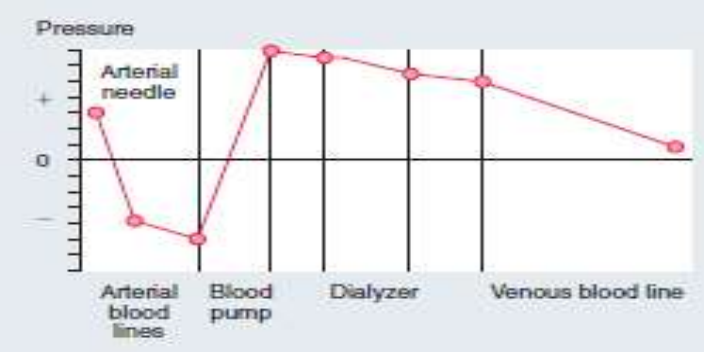
I) Blood Circuit Components:

- ❑ Arterial portion of blood circuit: Blood is pumped from the vascular access into the dialyzer through an arterial blood tubing.
- ❑ Blood pump: The blood is pumped by a peristaltic roller pump that sequentially compresses different segments of the tubing. The elastic tubing recoils after compression by the roller and refills with blood.

I)Blood Circuit Components:

- Pre-pump arterial pressure monitor: The hydrostatic pressure is negative between the vascular access and the blood pump. When the upper or lower pre-set pressure limit is exceeded, the system will trigger alarms, stop the blood pump, and clamp the venous tubing.
- Heparin: Is infused in the post-pump, pre-dialyzer segment of the blood circuit.
- Post-pump venous pressure monitor: The hydrostatic pressure in this segment is positive. When the upper or lower pre-set pressure limit is exceeded, the system will trigger alarms, stop the blood pump, and clamp the venous tubing.
- Venous bubble trap and air detector : When the air detector senses the presence of air, it triggers alarms, stops the blood pump, and clamps the venous tubing.
- Venous portion of blood circuit: Blood is returned from the dialyzer to the patient through the venous blood tubing.





II) Dialysate Circuit Components:

- Heating and deaeration:

  The purified water is heated to physiologic temperatures (35°C–38°C). The heated water is subjected to negative pressure to remove its air content. Air in the dialysate can impair flow in the dialyzer and cause the malfunctioning of blood leak and conductivity monitors.

- Proportioning:

  The heated and deaerated purified water is mixed with the dialysate concentrate in correct proportions.

  To prevent the precipitation of calcium and magnesium salts with bicarbonate, the dialysate is mixed from two separate concentrates:

1) The bicarbonate concentrate: sodium bicarbonate and sodium chloride.
2) The acid concentrate contains sodium, potassium, calcium, magnesium, chloride, and dextrose and a small amount of acetic acid.

II) Dialysate Circuit Components:

- A conductivity monitor

  Ensures proper proportioning of the dialysate with water. Conductivity is determined by the total ionic concentration of the dialysate. The normal range for conductivity is 12–16 ms/cm (millisiemens per centimeter).

- The temperature monitor:

  The dialysate temperature is usually maintained at 36°C–37°C.

  Cool dialysate, is sometimes used to prevent intradialytic hypotension by inducing vasoconstriction. An excessively warm dialysate can cause protein denaturation (>42°C) and hemolysis (>45°C).

- If the dialysis solution conductivity or temperature is out of range, the bypass valve is activated and the dialysate is diverted to the drain instead of entering the dialyzer.

II) Dialysate Circuit Components:

- The blood-leak detector:

  At the dialysate outflow segment detects blood in the dialysate.

  The presence of blood in the dialysate indicates rupture of the dialyzer membrane. When blood leak is detected, alarms are triggered and the blood pump is stopped.

- Ultrafiltration:

  Dialysis machines use volume-controlled ultrafiltration, which is much more precise in controlling the amount of fluid removed during dialysis.

  Volume-controlled ultrafiltration devices are mandatory for highflux dialyzers in order to prevent excessive fluid removal or dialysate backfilteration.

B) Hemodialysis Membranes

✓ There are two broad categories of membranes:

I) Cellulose based membranes (processed cotton)

a) Unsubstituted cellulose membranes:

- Cellulose which is made up of repetitive polysaccharide units containing hydroxyl groups.

- Regenerated cellulose and cuprammonium cellulose (Cuprophan) are examples of unsubstituted cellulose membranes.

- There are a large number of free hydroxyl groups on the cellulose polymer that are responsible for activation of the complement, the coagulation cascade, and cellular mechanisms (chronic inflammation). Activation of complement peaks at 15 minutes after the start of dialysis and lasts up to 90 minutes.

B) Haemodialysis Membranes

b) Substituted " modified" cellulose membranes:

- Chemical substitution of free hydroxyl groups on cellulose membranes.
- The free hydroxyl groups can be substituted by acetate (Cellulose Acetate), tertiary amino compounds (Hemophan).

II) Synthetic membranes :

- Are manufactured from non-cellulose synthetic polymers, so tend to be more biocompatible than cellulose membranes.
- Synthetic membranes in clinical use include polyacrylonitrile ,polyamide, polymethylmethacrylate , polysulfone, polycarbonate, or a combination of some of these polymers.

Membrane Efficiency

- M. Efficiency is defined as The ability of a dialyzer to remove the small molecules(urea). It is largely determined by the surface area (0.8- 2.1 m2).
- KoA "The dialyzer mass transfer area coefficient" is the calculated product of {the mass transfer coefficient (Ko) and membrane surface area (A)}.
- KoA is the theoretical maximum clearance of a particular solute for a given dialyzer when blood and dialysate flow rates are infinite.
- KoA is largely independent of blood solute concentration, blood flow rate, and dialysate flow rate.
- High-efficiency dialyzers have large surface areas and KoA values for urea >700 mL/min, while low-efficiency dialyzers have low surface area and KoA values for urea <500 mL/min.
- High-efficiency dialyzers can be high flux or low flux.

Membrane Flux

- Ultrafiltration coefficient (KUF):

  - Is defined as the volume of water transferred across the membrane per hour, for each mmHg of transmembrane hydrostatic pressure gradient.

  - The flux of a dialyzer is defined by the US FDA "Food and Drug Administration" according to its KUF.

- Water flux is largely determined by pore sizes, but membrane surface area is also a determinant.
- Dialyzers with KUF values >12 mL/h/mmHg are classified as high flux. Low-flux dialyzers usually have KUF values 2–5 mL/h/mmHg.

Membrane Efficiency vs. Membrane Flux

Membrane Efficiency:	○ Determined largely by membrane surface area. ○ Determines the ability of a dialyzer to remove small molecules (e.g. urea).
Membrane Flux:	○ Determined largely by membrane pore size. ○ Determines the ability of a dialyzer to remove middle molecules (e.g. β2-microglobulin) and water.

C) Hemodialysis Concentrate solution

- Dialysate is prepared by blending the properly **purified water** with HD **concentrates solution.**
- The typical concentrations of dialysate components:

Component	Concentration
Sodium	135–145 mmol/L
Potassium	2–4 mmol/L
Calcium	1.25– 1.5 mmol/L
Chloride	87–124 mmol/L
Magnesium	0. 5– 1.0 mmol/L
Bicarbonate	20–40 mmol/L
Acetate	2.0–4.0 mmol/L (higher in acetate dialysate)
Dextrose	0-11 mmol/L
pH 7.1–7.3	7.1–7.3

Sodium (135-145 mmol/L)

- Sodium is removed from the blood primarily by **convection** instead of **diffusion** during haemodialysis, so that there is little change in plasma sodium concentration. This is necessary to prevent hyponatremia or hypernatremia.
- **Sodium profiling or sodium modeling**:

  During this process, the dialysate sodium concentration at the beginning of the dialysis session is set at a higher value (e.g. 150- 160 mmol/L) with subsequent falls to a lower value (e.g. 135- 140 mmol/L) at the end of the session.
- **Sodium profiling** is designed to reduce intradialytic intravascular hypovolemia and symptomatic hypotension as well as the postdialysis washed-out feeling.

Potassium (2-4 mmol/L)

- The commonly used dialysate potassium concentrations are 2–3 mmol/L.
- If the patient is prone to cardiac arrhythmias or is on digitalis therapy, the use of a higher dialysate potassium concentration (≥3 mmol/L) is recommended.
- The use of 1 mmol/L potassium or potassium-free dialysate is associated with higher incidence of arrhythmias and should generally be avoided.

Calcium (1.25-1.5 mmol/L)

- In patients who are taking calcium-containing binders or active vitamin D analog, dialysates containing 1.25 mmol/L of calcium are usually used to avoid hypercalcemia or high plasma Ca × P product.
- A low dialysate **calcium concentration** may predispose the patient to intradialytic hypotension.
- Calcium-free dialysate has been used for the treatment of severe hypercalcemia or calciphylaxis; however, it is associated with cardiac arrhythmias and should be largely avoided.

Magnesium (0.25- 0.5)

- Hypomagnesemia and severe muscle cramps can occur with the use of magnesium-free dialysate.

Dextrose (5-10 mmol/L)

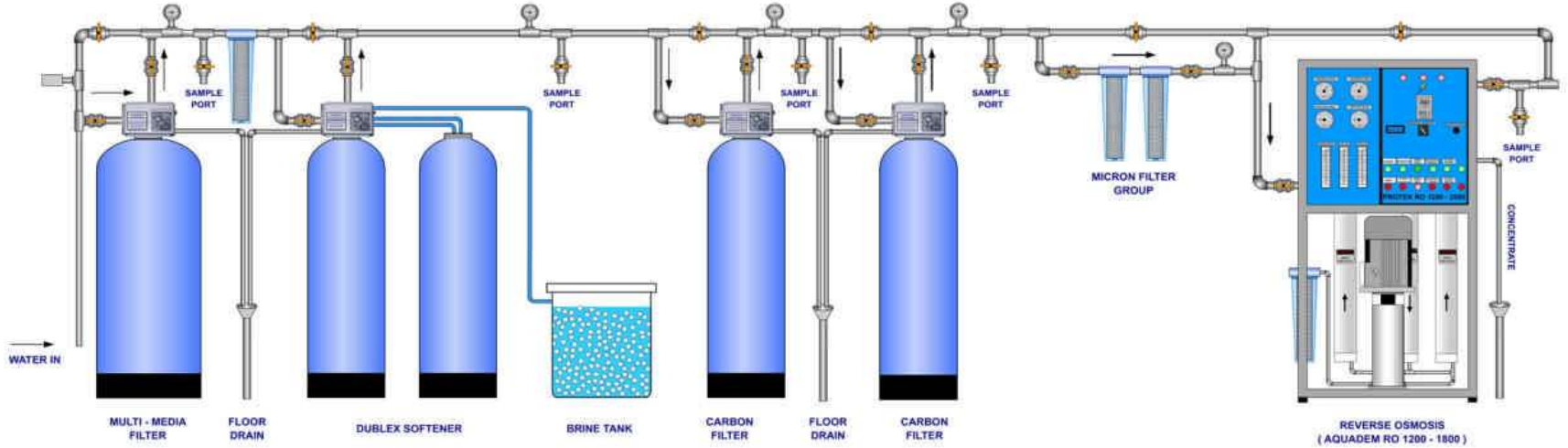
- Use of glucose-free dialysate may induce hypoglycemia in patients who are more prone to develop hypoglycemia (anti-diabetic medications).
- Glucose-free dialysates promote the loss of glucose and calories and, therefore, catabolism.
- High-glucose dialysate may impair the removal of potassium and phosphorus, also may lead to hyperglycemia and hyperinsulinemia.

Base

- A goal of HD is to provide base supplement in the form of **acetate** or **bicarbonate** to correct the **metabolic acidosis** with its consequences; decreased protein synthesis , increased protein catabolism and mineral and bone disorders.
- Acetate is converted into bicarbonate in many tissues in the body. It is associated with untoward effects including; hypoxemia, intradialytic hypotension, and an ill sensation .
- Bicarbonate levels in the dialysate are usually 32–39 mmol/L, in order to generate a positive bicarbonate balance and to keep the predialysis serum bicarbonate >22 mmol/L.
- Overalkalinization may result in reduced cerebral perfusion.

D) WATER TREATMENT FOR HEMODIALYSIS

- Water is considered as part of the prescription to the patient.
- Water makes >90% of the solution used for dialysis (dialysate). A standard 4-hour HD session exposes the patient to 120 to 200 liters of water. Only a semi-permeable membrane separates the patient's blood and dialysate (purified water and concentrate).
- Tiny amounts of chemicals and contaminants in the water has the potential to harm and can be dangerous to the patient.



D) WATER TREATMENT FOR HEMODIALYSIS

- **Feed Water Components:**

  a - Backflow- preventing device(BFD).

  b - Storage tank. c - Booster pump.

- **Pretreatment Components:**

  a - Sediment filters.

  b - Granular activated carbon filters..

  c - Water softener. d - Reverse osmosis.

- **Posttreatment components:**

  a - Ultraviolet (UV) treatment.

  b - Storage tank.

  c - Final filter (Bacterial).

  d - Booster pump e - Distribution pipes

D) WATER TREATMENT FOR HEMODIALYSIS

i) Sediment(Sand) Filter; to remove sand, clay, dust contaminants.

ii) Water softening; with the use of ion exchange, removes positively charged ions (calcium, magnesium and heavy metals) from the incoming water supply. The positively charged ions are replaced with sodium ions. The water softener protects and extend the life of the reverse osmosis membranes.

iii) Carbon filtration; is used to remove chlorine, chloramines, and low molecular weight organics through the process of adsorption.

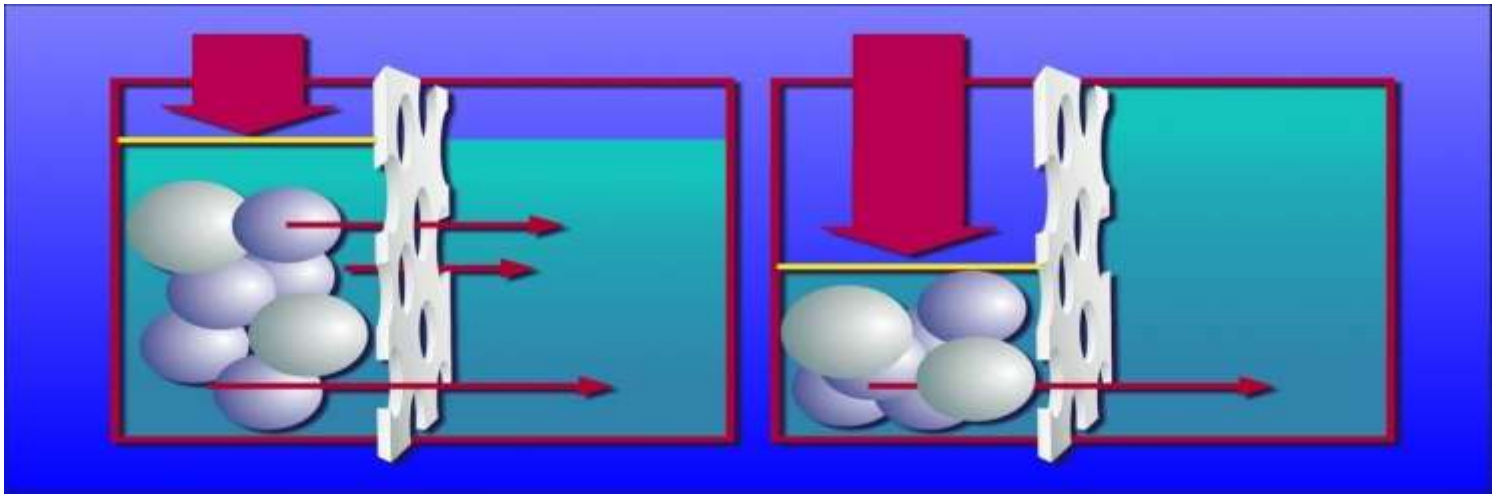
iv) Filters; (5,10,20,0.2, 0.1 M)are placed along the water treatment system to remove essential organics, bacteria and pyrogens.

v) Ultraviolet (UV) treatment.

WATER TREATMENT FOR HEMODIALYSIS

vi) Reverse Osmosis (RO):

- Entails forcing water through a very tight semipermeable membrane at very high pressure to remove the microbiologic contaminants and > 90% of the dissolved ions.
- Enough mechanical force (hydraulic pressure) with a pump is applied on the rejected water side; water is thus forced (filtered) against the osmolar force across the membrane.



The microbiologic standards for HD water

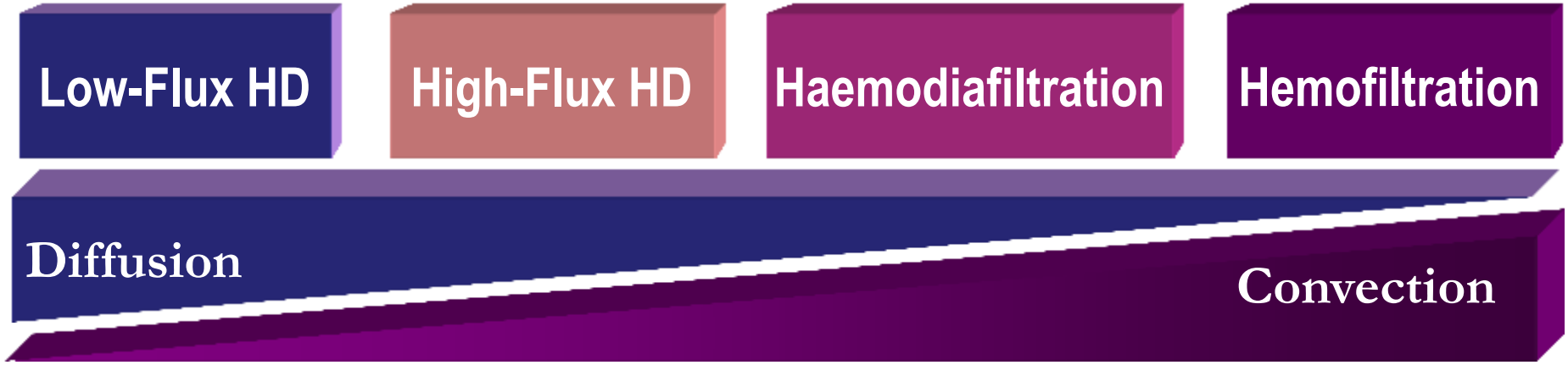
Recommendations for water quality for hemodialysis		
Fluid/Organization	Bacteria (cfu/ml)	Endotoxin (EU/ml)
Water for Hemodialysis		
AAMI	<200	<2
AAMI action level	50	1
UK Renal Association	<100	<0.25
European Best Practice Guidelines	<100	<0.25
European Pharmacopeia	<100	<0.25
Japan Society for Dialysis Therapy	<100	<0.25
Ultrapure water	<0.1	<0.03
Sterile water	<0.000001	<0.03

AAMI, Association for the Advancement of Medical Instrumentation

Standards for chemical quality of HD water

AAMI Standards	
Contaminant	**AAMI Suggested Maximum Levels**
Aluminum	0.010 mg/L
Antimony	0.006 mg/L
Arsenic	0.005 mg/L
Barium	0.100 mg/L
Beryllium	0.0004 mg/L
Cadmium	0.0010 mg/L
Calcium	2.000 mg/L
Chromium	0.014 mg/L
Copper	0.100 mg/L
Cyanide	0.020 mg/L
Fluoride	0.200 mg/L
Iron	N/A
Lead	0.005 mg/L
Magnesium	4.000 mg/L
Mercury	0.0002 mg/L
Nitrate (as N)	2.000 mg/L
pH	N/A
Potassium	8.000 mg/L
Resistivity	N/A
Selenium	0.090 mg/L
Silver	0.005 mg/L
Sodium	70.000 mg/L
Sulfate	100.00 mg/L
Thallium	0.002 mg/L
Total Dissolved Solids	N/A
Zinc	0.100 mg/L

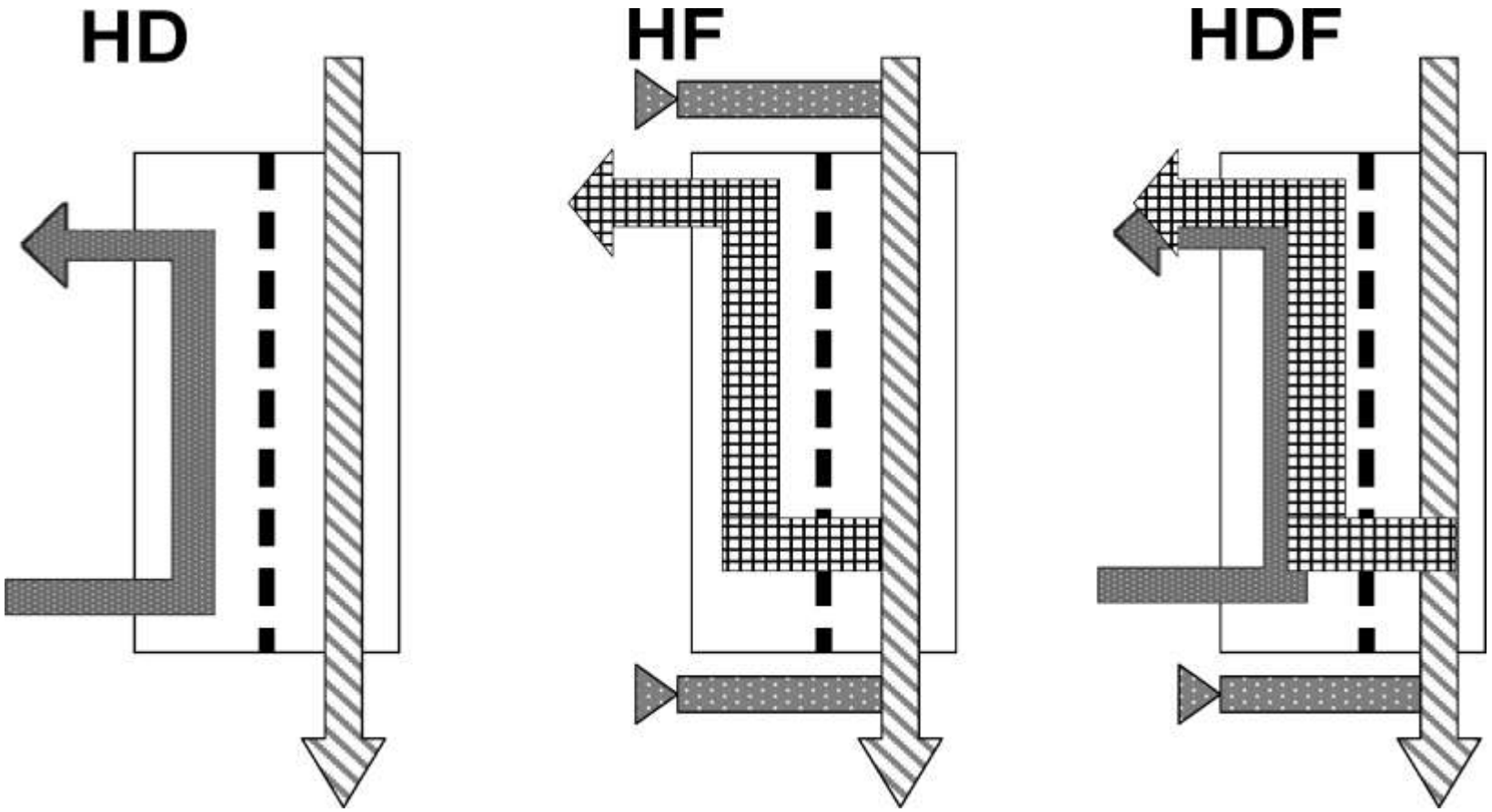
HDx Modalities



Hemofiltration(HF) and Hemodiafiltration(HDF)

- HF is primarily a dialytic technique by which solutes are removed by a convective transport imitating the filtration process in the glomerulus of natural kidneys within the limits of the pore size.
- HF; blood under pressure passes down one side of a highly permeable membrane, allowing both water and substances up to about 20 kd to pass across the membrane. During HF, the filtrate is discarded and the patient receives a substitution fluid either before (predilution) or after (postdilution) the dialyzer.
- HDF is a hybrid between HF and HD and incorporates a countercurrent dialysate solution within the hemofiltration circuit. With this procedure, low molecular substances are predominantly cleared by diffusion, while larger molecules are cleared mainly by convection .

Hemodialysis, Hemofiltration, Hemodiafiltration



Fluid route determines the mode of therapy

Evolution for Hemodiafiltration

- The evolution for HDF has become possible due to advances in the construction of dialysis membranes.(high-flux membrane, partially hydrophilic, high sieving coefficients, and a reduced wall thickness) have made it possible to combine diffusion and convection conveniently for blood purification.
- The second important step has been the development of accurate ultrafiltration control systems.
- The third step involves the production of large amounts of ultrapure dialysate.
- The fourth step with the online production of substitution (replacement) fluid has enabled high volume exchanges in HDF. This is a major breakthrough in reducing the treatment cost.

Evidence for Clinical Efficacy in Hemodiafiltration

1) Blood Purification: Excellent removal of small- and middle-sized molecules, including the amyloidogenic factor of β2M , Lower incidence of carpal tunnel syndrome.

2)Management of Anemia: Improved anemia management. Studies have shown a reduced need for erythropoietin. This may be related to an excellent treatment biocompatibility and/or to a superior solute removal.

3)Intratreatment Tolerance: Fewer hypotensive episodes, Lower incidence of muscle cramps and posttreatment fatigue, Suggested mechanisms include removal of the vasodepressor, less cytokine production, improved heat balance, and better blood volume preservation.

Evidence for Clinical Efficacy in Hemodiafiltration

4) Intertreatment Tolerance: Better blood pressure control, Improved intertreatment comfort.

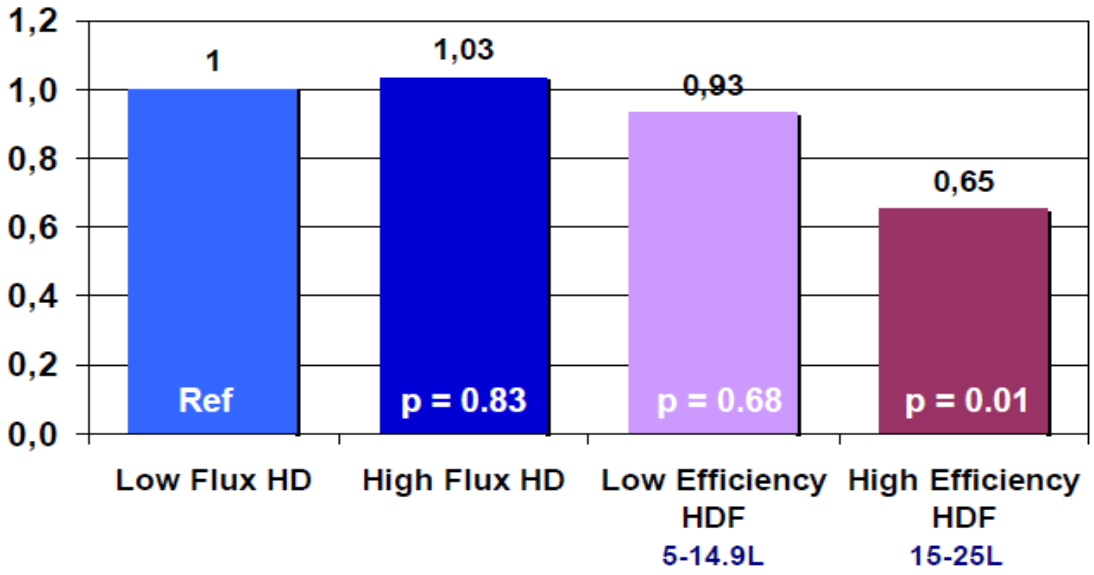
5)Residual Renal Function: Recent studies suggest that high-flux therapy contributes to a longer and better preservation of residual renal function than conventional hemodialysis.

6) Hospitalization: Reduced hospitalization, especially in high-risk patients like elderly patients and diabetics.

7) Mortality: No large-scale studies to demonstrate improved survival of patients on long-term convective dialysis therapies

Mortality risk is reduced for patients receiving HDF vs HD

Euro-DOPPS



DOPPS

Canaud B et al, *Kidney Int* 2006; 69: 2087-2093

Thank You

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7-2012